Remarks

Claims 28-43 are active in the application. Claims 28 and 37 are active and independent. Claims 16-18 and 21-23 are pending but withdrawn. Claims 1-15, 19, 20 and 24-27 are canceled without prejudice or disclaimer.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Interview of January 6, 2011

Applicants sincerely thank Examiner for the courteous and helpful interview granted to Applicants' representatives on January 6, 2011. At the interview, Applicants' representatives were granted an opportunity to discuss the rejections with the Examiner. Applicants' ***statement of the substance*** of the interview is provided below, and within the remarks in reply to the rejections.

The Invention

In brief review, and as discussed in the replies to the previous Office actions and at the interview, there was a need in the art for a freeze-dried form of methylcobalamin that could be used, *inter alia*, for the formulation of "high-concentration," *e.g.*, 0.5 to 1.5 mg/day, methylcobalamin injections for the treatment of diseases such as, for example, amyotrophic lateral sclerosis or other peripheral nerve disorders. Concentrated and freeze-dried forms of methylcobalamin do not have a good long-term stability. As mentioned in the background section on specification page 2, JP S62-38, S63-3137 and

H1-132514 disclose freeze-dried multi-vitamins preparations that included methylcobalamin but there were problems with these preparations including

- storage stability of freeze-dried preparations;

- a problem with the ability to re-dissolve the dried form in multivitamin preparations;

- photo-instability of concentrated methylcobalamin preparations; and

- a difficulty in guaranteeing the sterility of aqueous solution.

The invention embodies the discovery of a chemical environment that chemically stabilizes freeze-dried methylcobalamin in long term storage. The inventors discovered that freeze-dried high concentration compositions of methylcobalamin are very stable when the crystalline state of the excipient is suppressed, and specifically when stored freeze-dried with an excipient that comprises at least one sugar that is in an amorphous state, such sugar being selected from the group consisting of glucose, fructose, maltose, lactose, sucrose and trehalose, thereby arriving at the invention. Note that it is not required that the methylcobalamin itself be in the amorphous form, although it can be. Rather, it is sufficient if a sugar component of the excipient is in the amorphous form. The freeze-dried preparation of the invention that comprises a high content of methylcobalamin has

- has excellent stability over time and temperature; and

- can be used in high-concentration methylcobalamin therapy.

As shown below, the combination of the cited art does not detract from the non-obviousness of the invention.

The Art Cited in the Rejections under 35 U.S.C. § 103(a)

At Office action at page 3, claims 28-43 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Miyake *et al.,* (JP 63-313736; herein "Miyake") in view of Driskell, Sports Nutrition, CRC Press, page 75, (2000) (herein "Driskell"). Miyake is relied on as disclosing a preparation containing vitamin B_{12}, lactose, an antioxidant, and a pH adjuster which is then freeze-dried. The Examiner states that although Miyake refers B_{12} as "cyanocobalamin," as evidenced by Driskell, methylcobalamin is the active form of B_{12}. Thus, the Examiner asserts that it would have been *prima facie* obvious to replace cyanocobalamin in the formulation taught by Miyake with methylcobalamin in view of Driskell, and that in doing so, one would arrive at the claimed composition.

Applicants respectfully traverse the rejection, and Examiner's comments thereon, and respectfully request reconsideration.

Discussion

Miyake:

As discussed at the interview, Miyake is directed to a technique to improve the re-dissolution of multivitamin preparations containing both water soluble and fat soluble vitamins. Vitamin B_{12} (cyanocobalamin) is present in the preparations of Miyake.

Miyake's problem was that freeze-dried multivitamin preparations that contain a specific surface active agent, *e.g.*, a polyoxyethylene cured castor oil (to solubilize the fat

soluble vitamins) and an excipient such as lactose (to stabilize the water soluble vitamins during the initial freeze-drying process) could not be easily redissolved after freeze-drying. The preparations were turbid.

Miyake discovered that adding a polyhydric alcohol to a composition that contains the freeze-dried mixture of a polyoxyethylene cured castor oil and an excipient such as lactose, and the multivitamins, address the problem of turbidity that existed when such a preparation is re-dissolved. *See* Miyake, p. 8, lines 5-8 and Table 2. As such, the polyhydric alcohol is a necessary element in Miyake's preparations.

At the interview, the Examiner's attention was respectfully directed to the following:

- Miyake's control preparation contains, *inter alia,* lactose and cyanocobalamin.

  - Even assuming the freeze-dried lactose in Miyake's control preparation is in the amorphous form, Miyake's control preparation is unacceptable even for Miyake's purposes. The resolubilized control solution was turbid and the liquid "somewhat brown." (Miyake page 8).

  - Miyake does not report how long Miyake's solutions were stored in a freeze-dried form, or the conditions of storage. There is no discussion of long-term stability of the vitamins that are in Miyake's preparation, much less of a vitamin that is not in Miyake's preparation.

- There is no suggestion in Miyake that, even in Miyake's improved compositions, the presence of a polyhydric alcohol improved the stability of any of the active ingredients.

Driskell:

As discussed at the interview, Driskell is not directed to the problem of instability of freeze-dried methylcobalamin. Driskell simply states that vitamin B_{12} is a group of cobalamins or cobalt-containing corrinoids, including methylcobalamin, adenosylcobalim, and hydroxocobalamin, which have the biological activity of cyanocobalamin.

The Artisan Would not Have Substituted Methylcobalamin for Cyanocobalamin in the Preparation of Miyake Because They Are Different Compounds, With Different Properties, and Methylcobalamin is More Unstable

As discussed in the reply dated July 21, 2010, and during the interview on January 6, 2011, methylcobalamin and cyanocobalamin are different compounds and they have different properties.

The Examiner acknowledges that cyanocobalamin and methylcobalamin are distinct agents and that methylcobalamin is unstable, but asserts that a skilled artisan would not be deterred from substituting methylcobalamin for cyanocobalamin. No evidence supports the Examiner's reasoning and conclusion.

The Examiner asserts that the problem with stability "is due in part to formulating the preparation in a freeze-dried state." *See* Office action, p. 5.

As discussed at the interview, the Examiner's position seems to be that even if the skilled artisan would not have substituted methylcobalamin for cyanocobalamin in Miyake's control composition, it would be obvious for the person of ordinary skill in the art to substitute methylcobalamin in Miyake's preparations that include polyhydric alcohols, and that such components are not excluded by the compositions of the invention since Applicants' claims use "comprising" language.

Applicants respectfully disagree that there was any reason to substitute freeze-dried methylcobalamin for freeze-dried cyanobalamin in Miyake's preparation. Applicants respectfully assert that it is not necessary for Applicants' claimed invention to exclude unrelated components such as polyhydric alcohols, which are only an option in the claimed compositions in order to establish the non-obviousness of the claimed invention.

Applicants note that in Miyake, the closest composition to that of the invention is Miyake's control composition, which had unacceptable properties even for Miyake's use. The disclosure of Miyake leads a person of ordinary in the art away from the substitution proposed by the Examiner. Even though the individual components of the composition as claimed were known, and the combining steps were technically possible, an artisan of ordinary skill would not have undertaken Applicants' way of solving the problem of chemical instability of freeze-dried methylcobalamin because there was no recognized reason in the art to reach the solution that Applicants found. The claimed invention, when viewed as a whole, is more than simply substituting a known element for another. Applicants' result was not reasonable predictable based on Miyake in view of Driskell.

See "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex," 75 Fed. Reg. 53643 (September 2, 2010).

At the interview, Applicants discussed that under U.S. case law, a reference may teach away from an invention when it would destroy the teachings of the reference in order to reach the claimed invention. Applicants respectfully assert that to remove the polyhydric alcohols from Miyake would destroy it. By demonstrating the problems with a solution that contains freeze-dried lactose in combination with cyanocobalamin, Miyake discredits or otherwise discourages arriving at the claimed composition and especially as a solution for the problem that Applicants faced, and thus leads away from reaching the claimed invention. In this regard, the Examiner's attention is respectfully directed to *In re ICON Health and Fitness, Inc*, 496 F.3d 1374, 1381 (Fed. Cir. 2007) (citing *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001); *see also* National Steel Car, Ltd. v. Canadian Pam. Ry., Ltd., 357 F.3d 1319, 1339 (Fed. Cir. 2004) (reference teaching that combination would produce a seemingly inoperative device teaches away from the combination). When the prior art teaches away from a combination, that combination is more likely to be nonobvious.

The Claimed Invention is not Obvious to Try in View of Miyake in View of Driskell

Further, substituting methylcobalamin for cyanocobalamin cannot be characterized as being obvious to try in view of the cited art. An obvious to try rationale may be proper when the possible options for solving a problem were known and finite.

See "Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex," 75 Fed. Reg. 53643 (September 2, 2010).

However, here, the possible options for providing a solution to the problem of the long term chemical storage instability of freeze-dried methylcobalamin were unknown in view of the combination of the cited art. The combination of cited art does not provide a known or finite set of options for solving the problems faced by the present inventors.

Even assuming methylcobalamin is substituted for cyanocobalamin, a person of ordinary skill in the art would not arrived at the claimed invention. Miyake's preparation is a multivitamin preparation and Miyake addresses a problem unique to freeze-dried multivitamin preparations that contain polyoxyethylene cured castor oil and an excipient such as lactose. According to Miyake, the problem caused by the presence of the combination of an excipient and a polyoxyethylene cured castor oil derivative in the lyophilized preparation can be solved by either (1) eliminating the excipient/lactose (Miyake's background art) or by (2) adding a polyhydric alcohol to the preparation. Both of those solutions lead away from the invention since the invention not only utilizes an excipient but also the composition of the invention does not require a polyhydric alcohol, a component essential to Miyake's preparations. As stated above, modifying Miyake to remove polyhydric alcohols destroys the advantage of Miyake and results in Miyake's control preparation which was unacceptable for use even for Miyake (*e.g.*, CE1 in Table 2). *See* MPEP § 2143.01.

In addition, the claimed invention requires that at least one of the named sugars in the composition be in an amorphous state. Miyake merely states that the Miyake

preparations were freeze-dried; it does not indicate how the process was performed. Even assuming the lactose in Miyake's preparation was in an amorphous form, the art is silent that such form will affect the long-term freeze-dried stability of methylcobalamin. The art further lacks any suggestion that freeze-drying the active agent, methylcobalamin in an amorphous form would provide stability of the compound.

The amorphous sugar contained in the claimed composition keeps the methylcobalamin stable, both physically and chemically. And the stability can be further achieved by keeping methylcobalamin in an amorphous state. For example, as taught in the specification, and as mentioned at the interview, the residual ratio of the compound is 95% or more after no less than 2 years storage at room temperature, or after 6 months storage at 40 °C. *See* the present specification, pp. 15-16. It is unknown how long Miyake's preparations were in the freeze-dried form. Therefore, there's no suggestion that any long-term storage benefits of methylcobalamin may be obtained by the Miyake preparations.

In fact, the stability of methylcobalamin achieved by the claimed invention is unexpected in view of the art knowledge that drugs or chemicals in an amorphous state are unstable both physically and chemically. For example, Craig *et al., J. Pharmaceut. 179*: 179-207 (1999) (herein "Craig"), cited by the Examiner in the Office action dated July 22, 2009, states:

> Given the potential advantages of preparing drugs in an amorphous form, the question arises as to why this approach is not used more often. ***The single most important reason is undoubtedly the problems associated with stability, both physical and***

> ***chemical.*** The amorphous state is, by definition, metastable with regard to the crystalline material, hence amorphous drugs will tend to revert to the crystalline form over a period of time. Prediction of the timescales involved is clearly critical and yet may be difficult to achieve.

Craig, pp. 193-194 (emphasis added).

Thus, despite the knowledge in the art that discouraged the chemical amorphous form as a solution for stability problems, Applicants achieved stability, especially chemical stability of methylcobalamin by a preparation containing an amorphous sugar and methylcobalamin.

In summary, even though the components of the compositions were known, and the combining steps were technically possible, no one of ordinary skill would have undertaken Applicants' way of solving the problem of chemical instability of methylcobalamin because there was no recognized reason in the art to reach the solution that Applicants' found. The result achieved by the claimed invention was not reasonably predictable based on Miyake in view of Driskell. The possible options for stabilizing methylcobalamin, especially chemically stabilizing the compound, were unknown in view of the art. As discussed above, knowledge in the art such as the instability of methylcobalamin and the instability of amorphous form of chemicals in general, would lead a person of ordinary skill in the art away from modifying Miyake to arrive at the invention. And the long term stability achieved by the claimed invention is unexpected in view of the knowledge in the art. The discussion above has shown that the rational underpinnings that are the basis of Examiner's articulated reasoning do not ground a

conclusion of obviousness Therefore, Applicants respectfully assert that a *prima facie* case of obviousness of the claimed invention is not established, or if it has been established, it has been overcome.

Conclusion

Prompt and favorable consideration of this Reply is respectfully requested. All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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